PROJECT NO. Y-65-88
REPORT FILE

ORIGINAL

YOUNGER LABORATORIES
Biochemists . . . Pharmacologists . . . Analysts

128 CLIFF CAVE ROAD
ST. LOUIS 29, MISSOURI
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Certificate of Analysis

December 19th, 1963

SUBJECT -

Toxicological Investigation Of: NCS - 300

Monsanto Sample Number 112

Monsanto Project Number Y-65-88

STUDY CONDUCTED FOR -

Monsanto Chemical Company, St. Louis, Missouri

COPY

EXPERIMENTAL PROCEDURE -

A) Oral LD_{50} (Rats, Mixed Sex)

The undiluted compound was fed by stomach tube to Sprague-Dawley strain albino male and female rats.

After the approximate Minimum Lethal Dose was determined, groups of male and female rats were fed in increasing doses at increments of 0.1 fractional log intervals at four levels designed to blanket the toxicity range thereby supplying data for calculation of the LD_{50} which was done according to a modification of the method of J. W. Weil.

Observations were made for toxic symptoms and the viscera of the animals that succumbed were examined macroscopically.

The data are shown in Table I.

B) Skin Absorption MLD (Rabbits, Mixed Sex)

The undiluted compound was applied in increasing doses at increments of 0.2 fractional log intervals to the closely clipped, intact skin of New Zealand white male and female rabbits.

The treated areas were covered with plastic strips and the animals placed in wooden stocks for periods up to twenty-four hours, after which time they were assigned to individual cages.

Observations were made for toxic symptoms and the viscera of the animals that succumbed were examined macroscopically.

The data are shown in Table II.

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EXPERIMENTAL PROCEDURE - (Continued)

C) Skin Irritation (Rabbits)

The undiluted compound was applied to the clipped, intact skin of albino rabbits and removed after twenty-four hours. The application was covered with plastic strips to retard evaporation and avoid contamination.

Observations were made over a period of several days for irritation.

The data, scored according to the method of Draize, Woodard and Calvery (Journal of Pharm. and Exp. Therapeutics, Volume 82, December, 1944) are shown in Table III.

D) Eye Irritation (Rabbits)

0.1 Milliliter of undiluted sample was placed in the conjunctival sac of the right eye of each of three albino rabbits and observations made over a period of several days for inflammation.

The eyes were rinsed with warm isotonic saline solution after twenty-four hours.

The data, scored according to the method of Draize, et al, are shown in Table IV.

E) Vapor Inhalation (Male Rats)

Four 150-gram male rats were placed in a glass desiccator, 250 mm in diameter, and exposed for six hours to a concentrated atmosphere of vapors produced by passing a stream of air through 150 milliliters of the compound contained in a 250-milliliter tall form gas washing bottle with fritted disc. Vapors from the bottle passed into a one liter bottle to remove droplets and then into the chamber.

Air flow through the sample was 6 liters per minute as measured by a calibrated rotameter. This was sufficient to violently agitate the liquid. No supplementary air was introduced inasmuch as the above supply was ample for the animals oxygen requirements.

The animals were observed for behavior and, since there were no deaths, all were held for ten days observation.

The data are shown in Table V.

SUMMARY -

MCS-500

A) Oral LD_{50} (Rats, Mixed Sex)

The Oral LD_{50} for male and female rats was placed at 8,920 milligrams per kilogram with lower and upper limits of 7,045 to 11,325 milligrams per kilogram.

The compound was classed as practically non-toxic by oral ingestion in male and female rats.

B) Skin Absorption MLD (Rabbits, Mixed Sex)

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 3980 milligrams per kilogram and less than 6310 milligrams per kilogram.

The compound was classed as slightly toxic by skin absorption in male and female rabbits.

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SUMMARY - (Continued)

C) Skin Irritation (Rabbits)

The compound was classed as a moderate skin irritant when applied undiluted to intact rabbit skin.

The average maximum score was 4.3 out of a possible 8 in twenty-four hours.

D) Eye Irritation (Rabbits)

The compound was classed as a mild eye irritant.

The average maximum score was 19.6 out of a possible 110 in one hour.

E) Vapor Inhalation (Male Rats)

All animals survived the six hour exposure as well as the following ten day observation period.

It was concluded that the vapors were practically non-toxic under conditions of the test.

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BY: FRED M. YOUNGER

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TABLE I

THE ORAL LD_{50} OF 'MCS-300' FOR RATS

Sample Fed Undiluted

Animal No. - Sex	Weight Gm.	Dose Mg./Kg.	Fate
1- Female	220	6,310	Survived
2- Female	235	6,310	Survived
3- Male	230	6,310	Survived
4- Male	240	6,310	Died
5- Female	240	6,310	Survived
6- Female	225	7,940	Survived
7- Male	245	7,940	Died
8- Male	250	7,940	Died
9- Female	215	7,940	Survived
10- Female	220	7,940	Survived
11- Male	250	10,000	Died
12- Male	235	10,000	Died
13- Female	205	10,000	Survived
14- Female	215	10,000	Survived
15- Male	235	10,000	Died
16- Male	240	12,600	Died
17- Female	220	12,600	Survived
18- Female	225	12,600	Died
19- Male	235	12,600	Died
20- Male	240	12,600	Died

DISCUSSION -

The Oral LD_{50} for male and female rats was placed at 8,920 milligrams per kilogram with lower and upper limits of 7,045 to 11,525 milligrams per kilogram.

The compound was classed as practically non-toxic by oral ingestion in male and female rats.

Survival time was two to six days with most deaths occurring in two to three days.

Toxic symptoms included severe diarrhea, loss of appetite, increasing weakness and collapse.

At autopsy there was inflammation of the gastrointestinal mucosa with liver and renal hyperemia.

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TABLE II

THE MINIMUM LETHAL DOSE OF 'MCS-300'
BY SKIN ABSORPTION IN RABBITS

Sample Applied Undiluted

Animal No. - Sex	Weight Kg.	Dose Mg./Kg.	Weight Change 5 Days Later Kg.	Fate
1 - Female	2.2	1,000	0.0	Survived
2 - Male	2.5	1,580	- 0.2	Survived
3 - Female	2.2	2,510	- 0.2	Survived
4 - Male	2.4	3,980	- 0.4	Survived
5 - Female	2.3	6,310	- 0.3	Died — 5 Days
6 - Male	2.6	10,000	-----	Died — 3 Days

DISCUSSION -

The Minimum Lethal Dose by Skin Absorption in male and female rabbits was found to be greater than 3980 milligrams per kilogram and less than 6310 milligrams per kilogram.

The compound was classed as slightly toxic by skin absorption in male and female rabbits.

Survival time was three to five days.

Toxic symptoms included weakness, tremors, and muscular impairment after forty-eight to seventy-two hours.

At autopsy no visceral changes of consequence were noted, excepting for pulmonary hyperemia.

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TABLE III

SKIN IRRITATION IN RABBITS AFTER APPLICATION OF 'MCS-300'

Sample Applied Undiluted

Animal Number	Numerical Evaluation At The End Of					
	1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1	0	4	4	3	2	1
2	0	5	4	3	3	2
3	0	4	3	3	2	2
Average	0.0	4.3	3.6	3.0	2.6	1.6

DISCUSSION -

The compound was classed as a moderate skin irritant when applied undiluted to intact rabbit skin.

The average maximum score was 4.3 out of a possible 8 in twenty-four hours.

No skin changes were noted after one hour. Overnight there was well-defined erythema with slight to moderate edema for an average score of 4.3. No blistering developed but the edges of the treated areas were outlined by definite raising. Reduction of inflammation was gradual following removal of the application. After seven days slight redness and swelling were still present.

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TABLE IV

EYE IRRITATION IN RABBITS AFTER APPLICATION OF 'MCS-300'

Sample (0.1 Milliliter) Applied Undiluted

Animal Number	Numerical Evaluation At The End Of 1 Hour	24 Hours	48 Hours	72 Hours	120 Hours	168 Hours
1	18	16	11	7	2	0
2	18	13	9	4	0	0
3	23	18	13	9	4	0
Average	19.6	15.6	11.0	6.6	2.0	0.0

DISCUSSION -

The compound was classed as a mild eye irritant.

The average maximum score was 19.6 out of a possible 110 in one hour.

Discomfort was moderate immediately following application.

Mild redness of the conjunctivae, slight edema, little or no discharge, and slight corneal dullness developed within one hour for an average score of 19.6. Congestion decreased slightly in twenty-four hours. In five days, iris and cornea were clear and only a trace of erythema remained for an average score of 2.0.

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TABLE V

INHALATION OF 'MCS-300' VAPORS BY RATS

Average Temperature Inside Chamber ..... 77° F.

Average Relative Humidity Inside Chamber ..... 49 %

Amount Of Sample -- To Start ..... 150 cc
Recovered ..... 148 cc
Vaporized or left in the apparatus ..... 2 cc (1.3%)

Animal No. - Sex	Fate	Observations During Exposure
1 - Male	Survived	Mild lethargy after thirty to sixty minutes ...
2 - Male	Survived	No discomfort ...
3 - Male	Survived	Normal breathing rate ...
4 - Male	Survived	No inflammation.

DISCUSSION -

All animals survived the six hour exposure as well as the following ten day observation period.

It was concluded that the vapors were practically non-toxic under conditions of the test.

The animals appeared to be unaffected by the exposure. No signs of irritation or discomfort were noted during the test. Nasal and ocular mucosae were free of inflammation upon examination at the end of the six hours. The ten days observation period was uneventful.

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